



# Placebo effects: Scientific advance and potential clinical and ethical implications

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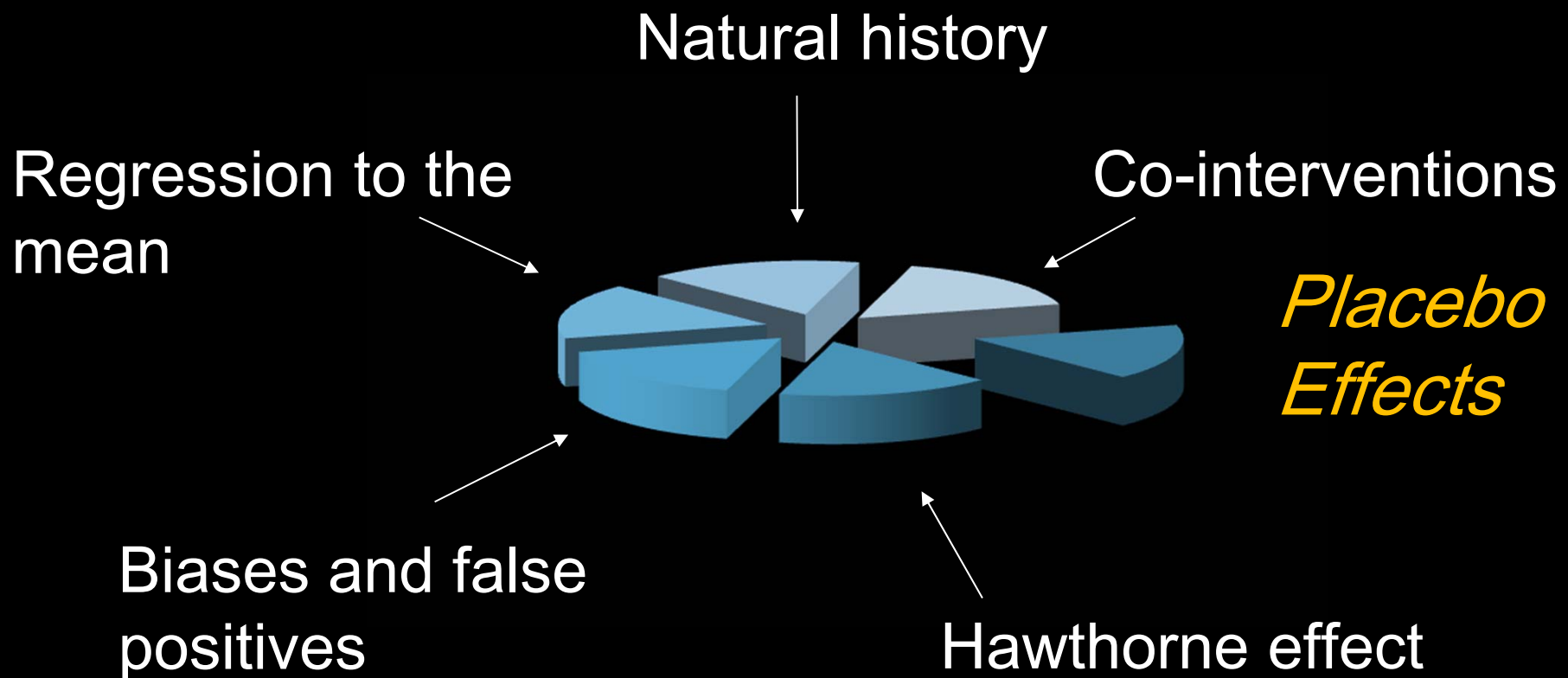


I do not have any financial interests relevant to this meeting, such as a financial relationship with any company or group that may be affected by the topic of this meeting

# Definitions

- **Placebo “I shall please”:** *Placebo domino in regione vivorum* psalm 116, 9th verse
- **Placebo effects:** Neurobiological and clinical changes that are distinct from biases, regression to the mean, natural history, and co-interventions (inclusion of a no-treatment group)
- **Placebo responses:** Unspecific changes in clinical outcomes that may result from patients' perception of the therapeutic intervention (absence of a no-treatment group)

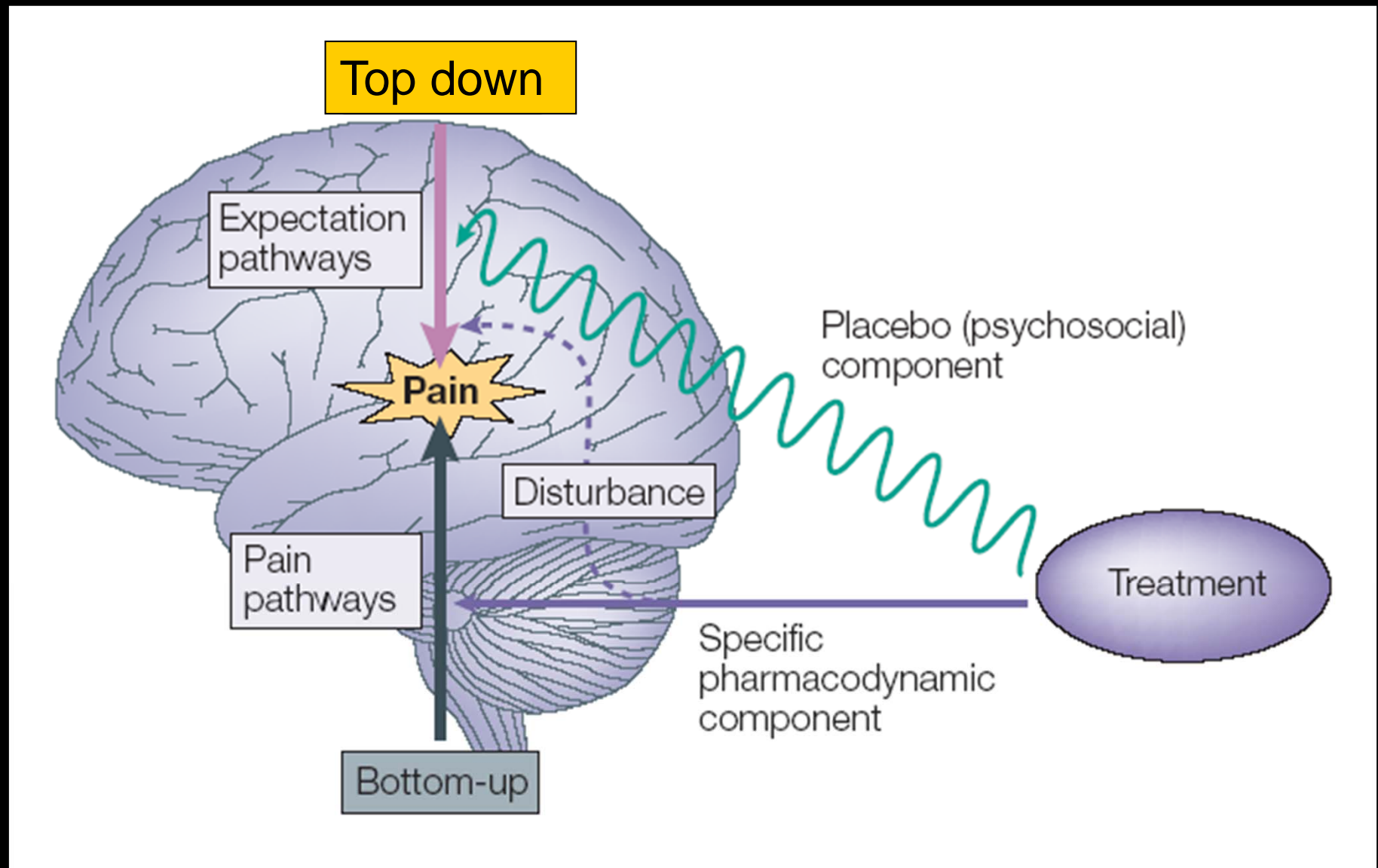
# How to identify a placebo effect...



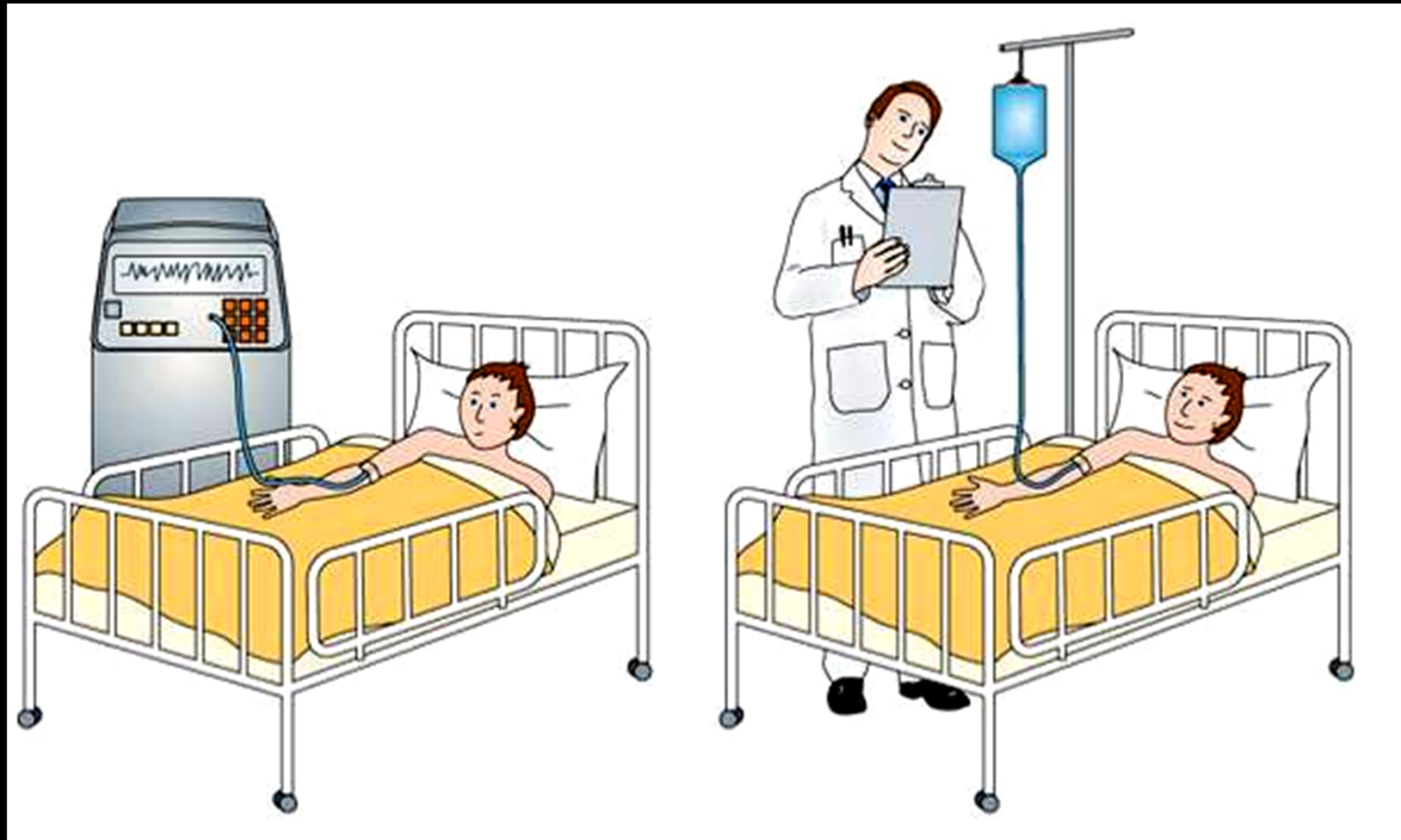
Colloca L, Benedetti F, Porro AC. Eur J Appl Physiol., 2008; 102(4):371-80

Colloca L, Finniss D, Benedetti F. Placebo and Nocebo. Hodder Arnold, 2008:499-513

# The placebo component of any intervention



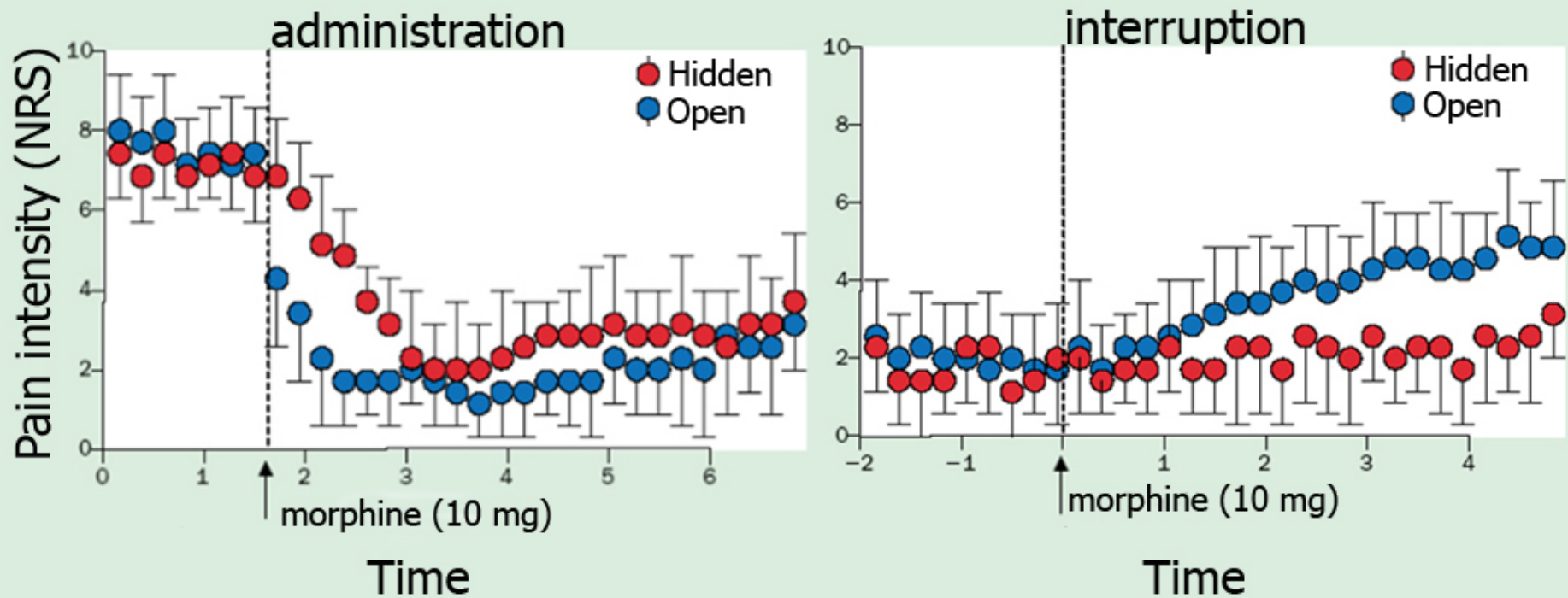
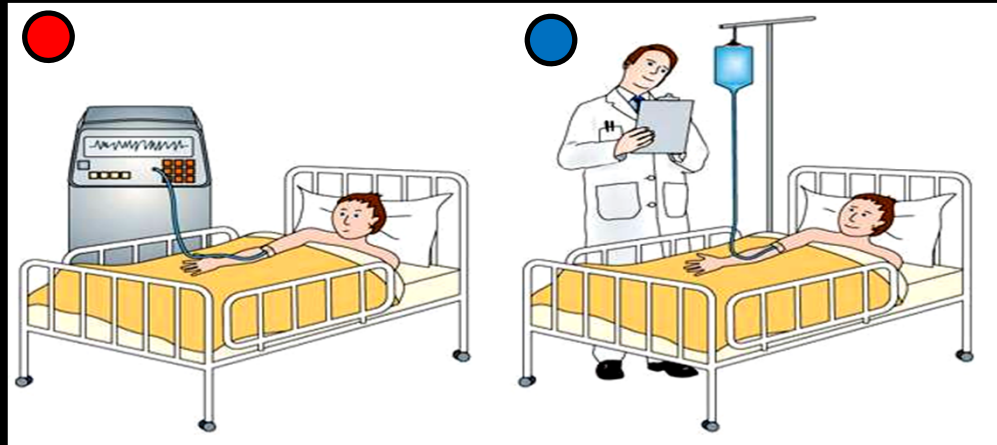
# Hidden versus open administration of medication



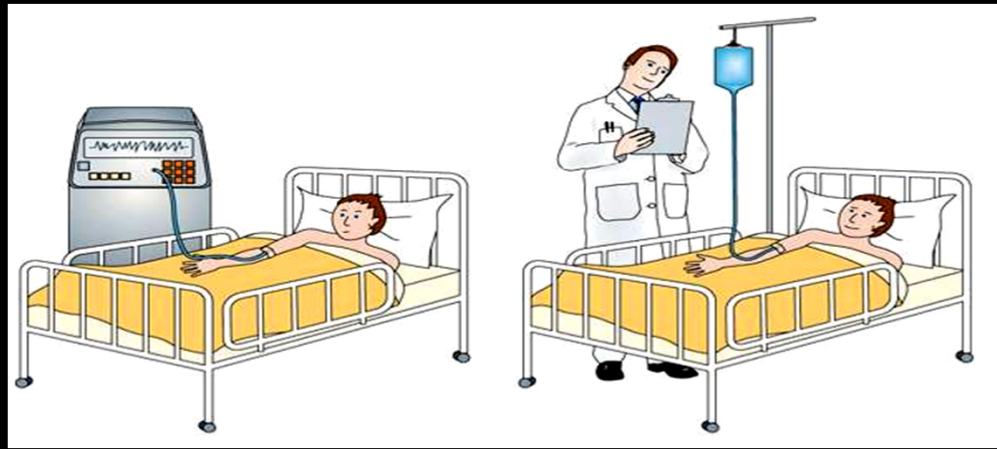
Enck et al. Nat Rev Drug Discov. 2013;12(3):191-204

# Positive and negative modulation of post-operative pain

Open-hidden  
paradigm

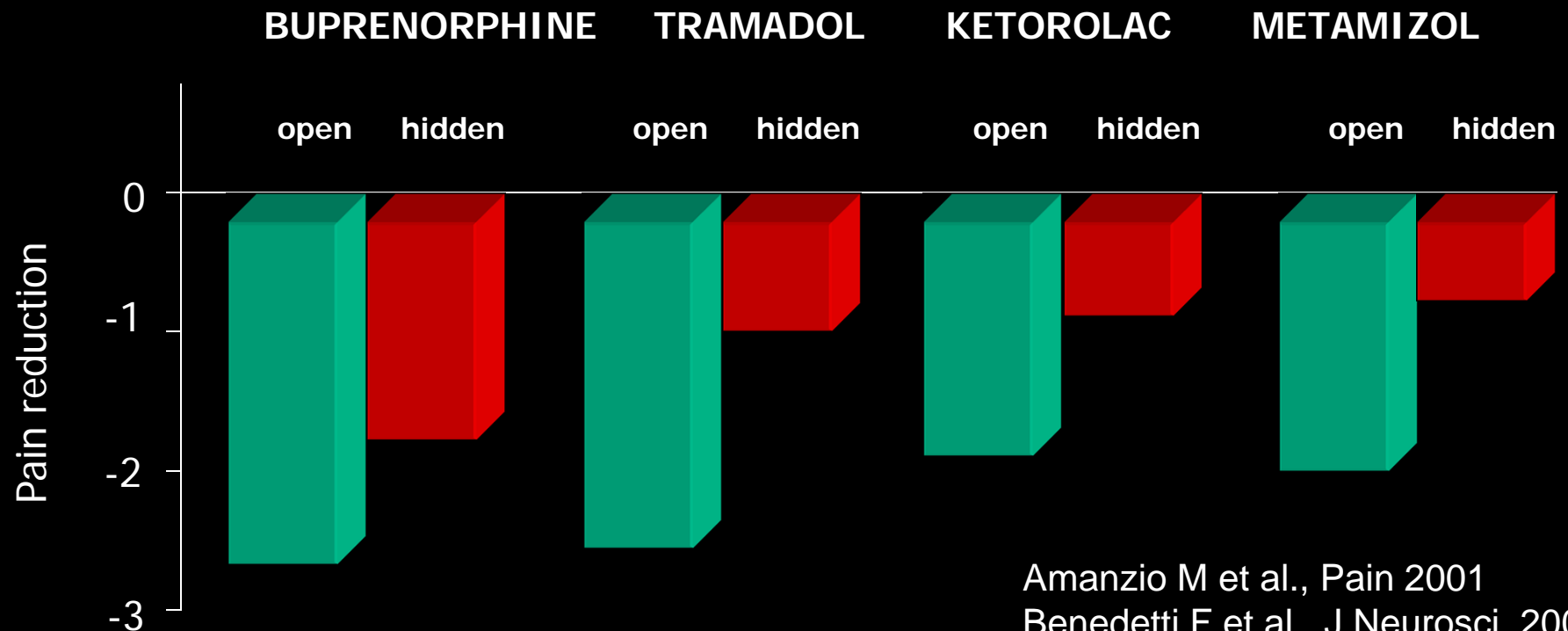


# Expectancy-induced analgesia and different painkillers



Open administration

Hidden administration



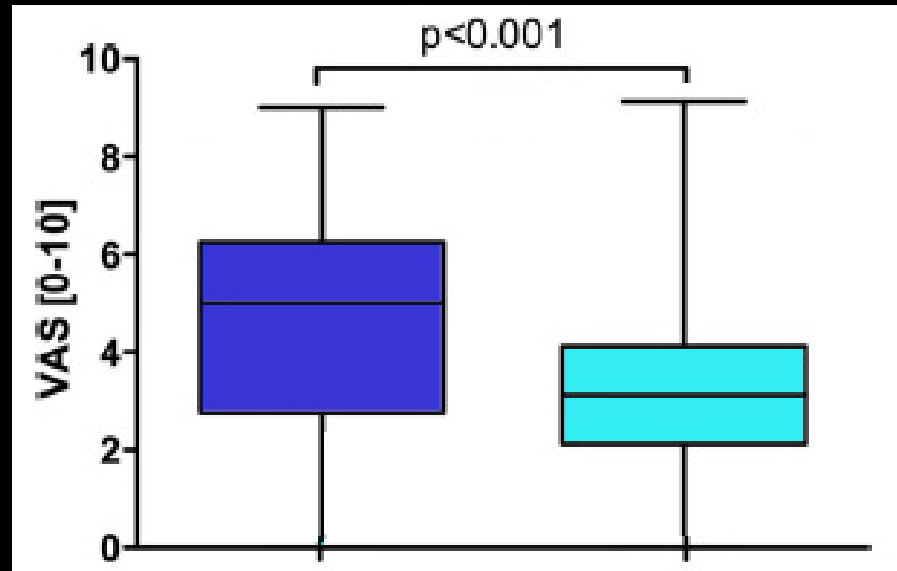
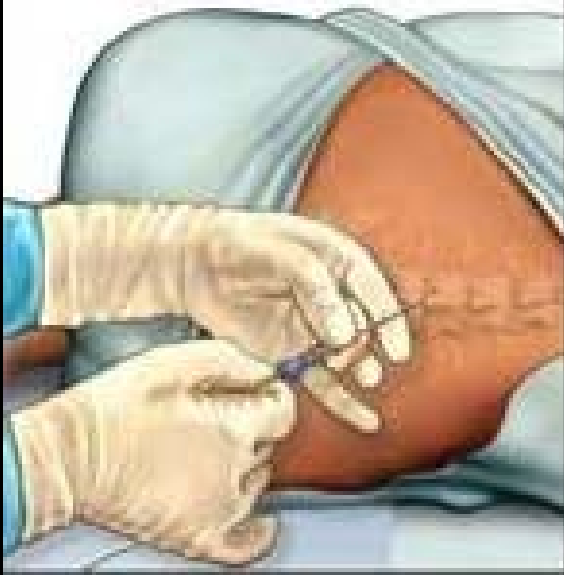
Amanzio M et al., Pain 2001

Benedetti F et al., J Neurosci, 2003

Colloca et al, Lancet Neurol., 2004



# Patient-clinician communication and placebo effects



**Group 1**

**Group 2**

**Group 1:** *“You are going to feel a big bee sting; this is the worst part of the procedure”*

**Group 2:** *“We are going to give you a local anesthetic that will numb the area and you will be comfortable during the procedure”*

# Patient-clinician interactions and placebo effects

- **Educate** clinicians and patients about the possible effects of placebo processes
- **Tailor** the information delivery process to the needs of the patient
- **Reframe** the disclosure process, continued attention to ethical approaches surrounding any disclosure

# What we have learned...

- Placebo effects depend upon the activation of **specific physiological mechanisms**
- Placebo research provides a hint to **reconsider the efficacy of interventions and treatments** that may work primarily on the basis of placebo mechanisms

# How do we identify effective interventions?

Any intervention has efficacy if it is demonstrated in RCTs to be superior to a placebo, no-treatment group and/or usual care interventions

- **If an intervention lacks specific efficacy,** is it still appropriate to recommend it in daily clinical practice?

## **Examples of lack of specific efficacy**

- Saw palmetto
- Vertebroplasty
- Homeopathy

# Saw palmetto

Serenoa repens extract, rich in fatty acids and phytosterols



- Used to treat a variety of conditions, most notably benign prostatic hyperplasia (BPH)

# Is saw palmetto effective in controlling BPH?

- Two large scale studies reported no difference in the primary outcome:

Saw palmetto vs finasteride (pts: 1098)  
37% vs 39 % symptom decrease

Saw palmetto vs tamsulosin (pts: 704)  
27% vs 28% symptom decrease

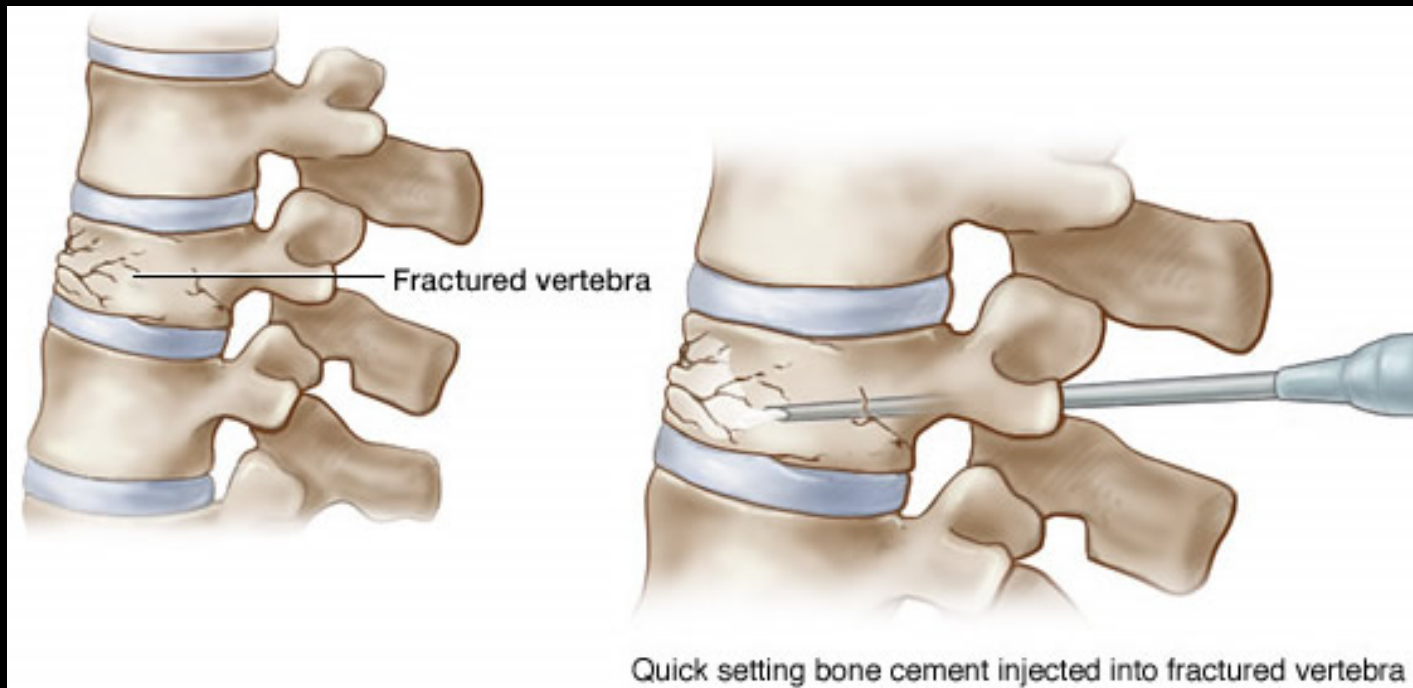
- Costs of saw palmetto are lower than finasteride and tamsulosin

Carraro et al. Prostate 1996; 29:231-40

Debruyne et al. Eur Urology 2002; 42: 497-507

# Vertebroplasty

Injection of cement into spine to stabilize vertebrae fractures



- Observational studies reported immediate pain relief and long-lasting benefit



# Is vertebroplasty superior than the sham one?

Sham vertebroplasty consists of a simulation of surgery without injecting any cement

- Results from 2 randomized clinical trials published on NEJM and one open-label trial published on Lancet report **no significant differences in pain between true and sham surgery at any measured time points.**

Klazen et al., Lancet 2010; 376(9746):1085-92

Buchbinder et al. NEJM 2009; 361(6):557-68

Kallmes et al. NEJM 2009; 361(6):569-79.

# Is it acceptable to recommend this intervention?

## Risk-Benefit-Cost profile

### ➤ **Safety**

No serious complications for sham vertebroplasty  
No difference in the occurrence of adverse events

### ➤ **Benefit**

But both true and sham vertebroplasty reduce patients' pain

### ➤ **Costs**

Patients treated with vertebroplasty gained on average 120 pain-free days

# Is the benefit of homoeopathy a placebo effect?

- Comparison between 110 homoeopathy trials and 110 matched conventional-medicine trials:

In large trials of higher quality, the odds ratio was 0.88 (95% CI 0.65–1.19) for homoeopathy and 0.58 (0.39–0.85) for conventional medicine

- A recent veterinary meta-analysis indicates no robust evidence that homeopathy is distinguishable from placebo effects in animals

Shang et al. Lancet 2005; 366:726-732

Mattie et al., Homeopathy 2015; 104:3-8

# Clinical and ethical considerations

- Are interventions working by virtue of placebo responses/effects clinically and ethically acceptable?
- Should clinicians recommend these interventions in addition to, but not instead of, conventional treatments?
- If interventions with equal efficacy than usual care are not given, do we deprive patients of potential benefits?

# Conclusive remarks

- It may be acceptable to recommend any intervention with clear favorable risk-benefit-cost profile
- In terms of professional integrity, it may remain potential conflict with evidence-based medicine
- Patients should be transparently informed about the lack of specific efficacy and a potential for unspecific placebo responses.

# Thank you for your attention

